Remarks

Claims 44, 54-74, and 77-80 previously were withdrawn from consideration by the Examiner as being drawn to a non-elected species, and are canceled herein. Claims 39-43, 45-53, 75, and 76 were under consideration in the office action mailed December 2, 2004. The Examiner has rejected claims 39-43, 45-53, 75, and 76 under 35 U.S.C. § 103(a) over Bhat *et al.*, in view of Tedder *et al.*, Anderson *et al.*, and Goldenberg. The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

Applicants have amended claims 39, 41, 43, 45, 50, 53, 75 and 76, and added claims 107-111. The amended claims are fully supported by the specification.

Support for Amendments

Applicants submit that support for the claim amendments and added claims is found throughout the specification and claims as originally filed. Support for the term non-blocking anti-CD22 antibody recited in claim 39, for example, is found in applicants' specification at page 13 (last sentence) to page 14 (first line). Additionally, at page 13 (second paragraph), the specification states "competitive blocking assays to determine CD22 epitope specificity are described by Stein *et al., Cancer Immunol. Immunother. 37*:293 (1993), and by Tedder *et al.*, U.S. patent No. 5,484,892 (1996). The cited Tedder patent states: "[T]he field of invention is directed to antibodies blocking the adhesion of erythrocytes and leukocytes to the CD22 receptor on mature B cells." *See column 1, lines 10-15 (emphasis added.*" In the context of the pending claims, therefore, the person of skill at the time of filing the present application would have understood the term non-blocking clearly to refer to blocking of cell adhesion.

Claims 39-43, 45-50, 52, 53, 75, 76, and 107-111 presently are pending for consideration.

Rejection under § 103(a)

The Examiner has rejected claims 39-43, 45-53, 75, and 76 based on the primary reference of Bhat *et al.*, Although Bhat describes, at most, a single antibody that purportedly binds to B-cells, the Examiner asserts that (a) Bhat is not limited to the use of one specific antibody and (b) the motivation and expectation of success for treating autoimmune disease are also provided by the secondary references. Applicants respectfully traverse.

A *prima facie* case of obviousness requires three elements: (1) a teaching or suggestion of all of the claim limitations; (2) a suggestion or motivation to modify or combine the teachings of the applied prior art; and (3) a reasonable expectation of success in reaching the claimed invention. Initially, the claims are presumed to be non-obvious; accordingly, the Examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. MPEP § 2142 (Feb. 2000).

Further, the Court of Appeals for the Federal Circuit has held that "[t]he consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this [claimed combination] should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art." *In re Dow Chem. Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Two requirements are contained in this criterion. The first requirement is that a showing of a suggestion, teaching, or motivation to combine the prior art references is an "essential evidentiary component of an obviousness holding." *C.R. Bard, Inc. v. M3 Sys. Inc.*, 157 F.3d 1340, 1352, 48 USPQ2d 1225, 1232 (Fed. Cir. 1998). This evidence may flow from: the prior art references themselves; the knowledge of one of ordinary skill in the art; or, in some cases, from the nature of the problem to be solved. *See Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1630 (Fed. Cir.1996). However, the suggestion more often comes from the teachings of the pertinent references. *See In re Rouffet*, 149 F.3d 1350, 1359, 47 USPQ2d 1453, 1459 (Fed. Cir. 1998). This showing must be clear and particular; broad, conclusory statements about the teaching of multiple references, standing alone, are not "evidence." *See In re Dembiczak*, 175 F.3d 994, 1000, 50 USPQ2d 1614, 1617, *abrogated on other grounds by In re Gartside*, 203 F.3d 1305, 53 USPQ2d 1769 (Fed. Cir. 2000).

The rejection here fails to satisfy the obviousness test. First, contrary to the Examiner's assertion, Bhat does not teach methods for inducing cell death in B-cells by employing reagents that bind to a B-cell marker, nor does Bhat teach or suggest that antibodies, other than CDIM, are useful for B cell depletion.

Specifically, Bhat states that B-cells may be defined by expression of surface markers such as CD19, CD20, and CD22 but, contrary to the Examiner's assertion, fails to teach or suggest that antibodies against these markers might be used to treat autoimmune disease. Despite

Bhat's recognition that B-cells express CD19, CD20, and CD22, nowhere does Bhat teach or suggest using antibodies against CD22 or CD20 to treat autoimmune disease. Further, although Bhat asserts that an antibody that binds CDIM might be used to treat autoimmune disease (see column 3, lines 25-27), no data are provided in support of this proposition. This deficiency is not remedied by any of the secondary references. In the absence of any data that the CDIM antibody is useful for treating autoimmune disease the person of ordinary skill in the art would not have had a reasonable expectation of success in using the CDIM antibody, or any other B-cell antibody, for treating autoimmune disease. Indeed, as explained in more detail below, the data provided by Bhat regarding the binding specificities of the CDIM antibody would not have led the person of ordinary skill to believe that anti-B-cell antibodies would be useful for treating autoimmune disease.

The pending claims recite methods for treating autoimmune disease using a composition comprising a non-blocking anti-CD22 antibody. The only suggestion that antibodies against CD19, CD20, and/or CD22 can be used to treat autoimmune disease is based on applicants' own specification. The use of applicants' specification in this manner is specifically the type of hindsight reconstruction of the claimed invention that is proscribed by the Federal Circuit:

> As this court stated, "virtually all [inventions] are combinations of old elements." *Environmental Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 698, 218 USPQ 865, 870 (Fed. Cir. 1983); *see also Richdel, Inc. v. Sunspool Corp.*, 714 F.2d 1573, 1579-80, 219 USPQ 8, 12 (Fed. Cir. 1983) ("Most, if not all, inventions are combinations and mostly of old elements"). Therefore an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint to defeat the patentability of the claimed invention. Such an approach would be an "illogical and inappropriate process by which to determine patentability." *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570, 38 USPQ2d 1551, 1554 (Fed. Cir. 1996).

As demonstrated above, Bhat fails to disclose the elements of the rejected claims for which it is cited by the Examiner. None of the accompanying references cited in the obviousness

rejections cure the shortcomings of the Bhat reference. Accordingly, the first element of a *prima facie* case of obviousness has not been satisfied.

The person of ordinary skill in the art also would not have had a reasonable expectation of success in using B-cell antibodies to treat autoimmune disease and therefore the third prong of the test for a *prima facie* case of obviousness also is not met. Specifically, the person of ordinary skill in the art would not have a reasonable expectation that the methods described in Bhat would be successful for treating autoimmune disease by inactivating or depleting B-cells, because the antibody described by Bhat was described as binding to other antigens, including red blood cell antigens.

As applicants have previously described, Bhat *et al.*'s antibody is not B-cell specific and would not have taught or suggested to one or ordinary skill the use of B-cell specific antibodies to treat autoimmune disease. Indeed, it is clear that Bhat's antibody is polyreactive and likely to be of no clinical use. The polyreactivity of the Bhat antibody is described in detail in Bhat *et al.* (1993), *Human antilipid A monoclonal antibodies bind to human B cells and the i antigen on cord red blood cells*, J. Immunol., Vol. 151(9): 5011-5021 (Exhibit A of applicants' October 13, 2004 Reply). This failure of Bhat to teach a B cell specific antibody raises further concern about the therapeutic usefulness and success of Bhat's alleged teaching.

The 1993 publication of Bhat *et al.* -- showing that the CDIM antigen is present on cord red blood cells -- would have led one of ordinary skill in the art away from using the CDIM antibody antibody as an *in vivo* therapy. The declaration of Dr. Don L. Seigel appended hereto provides further explanation as to why the antibody would be recognized as being completely unsuitable for any *in vivo* therapy. *See Declaration of Dr. Don L. Siegel,* appended hereto as APPENDIX A.

Specifically, one of ordinary skill in the art would have appreciated the potential harm in delivering a non-specific antibody as an *in vivo* therapy, particularly when the antibody apparently binds to antigens present on red blood cells. The recognition of this potential harm would have led one of ordinary skill in the art to recognize that Bhat's methods would not work for the purported purpose of treating autoimmune disease. Nothing in the teachings of Tedder *et al.*, Anderson *et al.* and Goldenberg, alone or in combination would cure the deficiencies of Bhat in this regard.

In sum, the clear deficiencies of Bhat mean that one of ordinary skill in the art would not have been motivated to use an anti-B-cell antibody for treating an autoimmune disease. Nor would the person of skill in the art following the alleged teachings Bhat have had a reasonable expectation that using anti-B-cell specific antibodies for treating autoimmune disease would be successful. The Examiner has failed to set forth any proper motivation to combine the cited references and relies upon an improper hindsight reconstruction of applicants' invention in setting forth the instant rejection. Moreover, even if a motivation to make the combination could be found, there would have been no reasonable likelihood of success in the combination. Accordingly, the Examiner has failed to establish a *prima facie* case of obviousness and the applicants respectfully submit that rejection should be withdrawn.

By contrast, applicants append below data from two ongoing human studies demonstrating the efficacy of the instantly claimed invention. With respect to the treatment of Sjogren's Syndrome, applicants have provided a paper copy of a slide presentation titled: "Initial Study of Humanized Anti-CD22 Monoclonal Antibody, *hLL2* (Epratuzamab) in Primary Sjogren's Syndrome (*APPENDIX B, attached hereto*) and a counterpart Abstract titled: "Initial Clinical Study of Immunotherapy In Primary Sjogren's Syndrome With Anti-CD22 Monoclonal Antibody Epratuzamab (*APPENDIX C, attached hereto*). The data presented in these documents are from a completed study in which fifteen individuals afflicted with primary Sjogren's Syndrome were treated with a humanized anti-CD22 antibody monoclonal antibody (*hLL2* - Epratuzamab). As the data demonstrate, anti-CD22 antibody is an effective *in vivo* human therapy for an autoimmune disease, Sjogren's Syndrome.

Similarly, use of Epratuzumab for the successful treatment of systemic lupus erythematosus (SLE) is demonstrated by the data in the study titled: "Pilot Phase II Study of Humanized Anti-CD22 Monoclonal Antibody, hLL2 (Epratuzumab), in Systemic Lupus Erythematosus Therapy" (*APPENDIX D, attached hereto).*

CONCLUSION

In view of the above remarks and amendments, it is respectfully submitted that this application is in condition for allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to telephone the undersigned at the number listed below if the Examiner believes such would be helpful in advancing the application to issue.

If any additional fees are required for the filing of this paper, applicants authorize the Commissioner to charge any deficiency to Deposit Account No. 08-1641.

Respectfully submitted,

Date: March 28, 2005

By 

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OIPE JC35
MAR 28 2005
PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of:
Goldenberg *et al.*

Confirmation No.: 3453

Application No.: 09/590,284

Art Unit: 1644

Filed: June 9, 2000

Examiner: Ilia Ouspenski

For: **IMMUNOTHERAPY OF AUTOIMMUNE DISORDERS USING ANTIBODIES WHICH TARGET B-CELLS**

DECLARATION UNDER 37 C.F.R. §1.132

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

I, Don L. Siegel, Ph.D., M.D., being duly warned, hereby declare and say:

1. I am Associate Professor & Vice-Chair of the Department of Pathology & Laboratory Medicine at the University of Pennsylvania.

2. I have a Ph.D. degree from Harvard University and an M.D. degree from the University of Pennsylvania . I am the principal author of numerous articles related to human monoclonal autoantibodies and alloantibodies. My *curriculum vitae* is attached.

3. I am being compensated for preparing this declaration at my normal consulting rate.

4. I have reviewed the Official Action dated December 27, 2004 in the captioned application. I also have reviewed U.S. Patent No. 5,593,676 ("the Bhat patent") and Bhat *et al.* (1993), *Human antilipid A monoclonal antibodies bind to human B cells and the i antigen on cord red blood cells*, J. Immunol., Vol. 151(9): 5011-5021 ("Bhat *et al.*").

5. I am informed that there is a two-part test for determining whether a claim is obvious. This test requires considering whether the prior art (i) would have suggested to one of ordinary skill in the art that the claimed invention should be carried out and (ii) would have had a reasonable likelihood of success, viewed in the light of the prior art.

6. The Examiner states that Bhat contemplates using anti-B cell antibodies to treat autoimmune diseases, such as multiple sclerosis. See Office Action at page 4. I disagree with the Examiner's characterization of the Bhat patent with respect to treatment of multiple sclerosis, for the reasons below. Also, it is my opinion that one of ordinary skill in the art would not have had a reasonable likelihood of success in using anti-B-cell antibodies for treating autoimmune disease based on the teachings of the Bhat patent.

7. The only reference to multiple sclerosis in the Bhat patent is at column 1, lines 33-40:

> These autoimmune diseases can be extremely destructive, as is evidenced by diabetes, rheumatoid arthritis, neuronal diseases, such as multiple sclerosis, and the like. While in many cases, the disease is associated with T-cell attack, in some of the diseases, there may be a B-cell component, and in other diseases, such as rheumatoid arthritis and lupus nephritis, the primary mediator may be B-cells.

This reference to multiple sclerosis clearly is in the context of a T-cell mediated disease and does not contain any suggestion that multiple sclerosis is a B-cell mediated disease. One of ordinary skill in the art would have read this paragraph in the context of the prevailing view in immunology that multiple sclerosis is a T-cell mediated autoimmune disease. Accordingly, it is my view that Bhat would not have suggested to one of ordinary skill in the art that multiple sclerosis might be a B-cell mediated disease.

8. Further review of the Bhat patent and Bhat *et al.* demonstrates that the data presented by Bhat would not have provided one of ordinary skill in the art with a reasonable expectation that autoimmune disease could be treated using an anti-B cell antibody.

9. First, it is clear that the 216 antibody described in the Bhat patent is not B-cell specific. See, for example, the description at column 6, lines 35-55 of the Bhat patent that shows that the 216 antibody binds to the *i* and *I* antigens present on red blood cells. One of ordinary skill in the art would not have been motivated to treat an autoimmune disease with a non-specific antibody that binds to red blood cells. Moreover, even if the person of ordinary skill tried to use the 216 antibody for treating autoimmune disease there would not have been a reasonable expectation of success because of the lack of specificity of Bhat's 216 antibody.

10. The lack of binding specificity of the '216 antibody is further demonstrated in the Bhat article that describes that 216 is a polyreactive antibody. Thus, for example, the abstract of

the Bhat article describes that 216 binds to "the lipid A domain of bacterial LPS" together with "the i Ag present on cord RBC, a ligand on human B lymphocytes and to certain autoantigens." Upon reading the Bhat article one of ordinary skill in the art would not have been motivated to use the 216 antibody for treating any B-cell mediated disease, let alone autoimmune disease, because of the antibody's polyreactivity. Moreover, this polyreactivity would not have led to any reasonable expectation of success in treating autoimmune disease.

11. The Bhat patent also states that the 216 antibody was isolated by incubating lymphocytes from a patient with nodular lymphoma with LPS and fusing the lymphocytes to a heteromyeloma cell line. See column 4 at lines 35-38. Accordingly, it appears that the lymphoma patient already produced the 216 antibody. Bhat *et al.* states that the patient had Hodgkin's lymphoma. See page 5102, left column, last full paragraph. Hodgkin's lymphoma is a B-cell lymphoma.

12. The fact that a patient suffering from a B-cell lymphoma produced the 216 antibody would provide further confirmation to one of ordinary skill in the art that the antibody would not be effective for treating B-cell mediated disease. Specifically, the fact that the patient suffered from a disease caused by B-cell proliferation while producing the 216 antibody demonstrates that the antibody is ineffective in suppressing B-cell proliferation *in vivo*.

13. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent resulting therefrom.

_____ _____

Date Don L. Siegel, Ph.D., M.D.

INITIAL CLINICAL STUDY OF IMMUNOTHERAPY IN PRIMARY SJÖGREN'S SYNDROME WITH HUMANIZED ANTI-CD22 ANTIBODY EPRATUZUMAB

S. D. Steinfeld[1], S. Rommes[1], L. Tant[1], I. Song[2], G. R. Burmester[2], W. A. Wegener[3], J. Kovacs[3], I. D. Horak[3], D. M. Goldenberg[3]

[1]Rheumatology, Erasme University Hospital, Brussels, Belgium, [2]Medicine, Rheumatology and Clinical Immunology, Charite Hospital, Berlin, Germany, [3]Immunomedics, Inc., Morris Plains, NJ, United States

Background: B-cells play important roles in the pathogenesis of autoimmune disease including primary Sjögren's Syndrome (pSS). Prior studies demonstrated the safety and efficacy of anti-CD22 immunotherapy in patients (pts) treated with epratuzumab for B-cell malignancies and SLE.

Objectives: An open-label, non-randomized study was conducted to assess feasibility, safety and early evidence of efficacy with epratuzumab in pts with pSS.

Methods: Fifteen Caucasian pts (13F/2M, 33 - 72 y.o.) meeting American European Consensus Group revised criteria for pSS, and with active disease at study entry (median ESR 30 mm/hr, gammaglobulins 2.5 gm/L), received 360 mg/m2 epratuzumab IV with antihistamine/acetaminophen premedication every 2 wks for 4 doses. The pts were 1-16 yr (median 2.3) beyond initial diagnosis, and had been on symptomatic treatment for >6 mo. No pt had prior rituximab or other B-cell targeted therapies and none were on steroids or immunosuppressives at study entry. Pts were followed over 12 wks with evaluations for safety, pSS activity (Schirmer I test, salivary flow, tender joint/point counts, irritated eye, dry mouth or fatigue levels, autoantibodies, other labs), and peripheral blood levels of epratuzumab, B & T cells, immunoglobulins, and human anti-epratuzumab antibodies (HAHA).

Results: All pts completed the study. Fourteen pts received all 4 infusions without reactions with a median infusion time of 50 min (25 -150 min), while one pt with an acute reaction discontinued 3rd inf. Three non-drug related serious events occurred (dental abscess, TIA, osteoporotic fracture) and 3 pts had non-serious events considered at least drug related (arthralgia, nausea/abd. pain, hypotension, palpitations, parathesia). B-cell values decreased post-treatment, but T-cell levels, immunoglobulins, and routine safety laboratories were not significantly changed. Epratuzumab serum levels varied across pts (Cmax 67-245 μg/mL), but without substantial increase across successive infusions, and with 7-10 day half-lives after 4th inf. Of 14 pts with evaluations at 4th infusion available, 10 pts had lacrimal flow increases (1-10 mm/5 min) and 5 pts had salivary flow increases (0.2-0.9 mL/15 min), while patients symptomatic at study entry reported clinical improvement of their dry/irritated eyes (7/12 pts), dry mouth (5/14), or fatigue (9/14), tender point (6/9) or joint (7/7) counts. Most responses are continuing with assessment levels 4 and 12 wks later remaining improved from baseline.

Conclusion: 360 mg/m2 epratuzumab appears safe and well-tolerated when administered every other week for 4 doses, with infusions typically < 1 hr duration. Initial efficacy results support apparent clinical improvement at early post-treatment evaluations with subsequent evaluations continuing to assess response durability.

EULAR2005 Abstract #1950. Submitted January 31, 2005 by WAW

Initial Study of Humanized Anti-CD22 Monoclonal Antibody, *h*LL2 (Epratuzumab) in Primary Sjögren's Syndrome

S.D.Steinfeld[1], S.Rommes[1], I.-H. Song[2], G.R. Burmester[2] W. A. Wegener[3], I. D. Horak[3], J Kovacs[3], C Ding[3], M.U. Qidwai[3], W Hoff[3], D.M. Goldenberg[3,4]

[1]Department of Rheumatology, Erasme Hospital, Brussels, Belgium, [2]Department of Medicine/Rheumatology and Clinical Immunology, Charite Hospital, Berlin, Germany, [3]Immunomedics, Inc., Morris Plains, NJ, [4]Garden State Cancer Center, Belleville, NJ

Immunomedics, Inc

Rationale / Objectives

- B-cells Play Important Role in Pathogenesis of Autoimmune Disorders
- First Pilot Study of anti-CD22 Mab, *h*LL2 (Epratuzumab, Immunomedics, Inc.), in Sjögren's Syndrome
- Study Objectives:
  - Confirm Safety,Tolerance and Lack of Immunogenicity in This Population
  - Evaluate Early Evidence of Efficacy
  - Assess Pharmacokinetics and Pharmacodynamics

Study Design

- Open-Label, Non-Randomized Study
- ~15 Pts
- Screening/Baseline Evaluations
- 360 mg/m^2 epratuzumab q 2 wks X 4 Doses; All Pts Premedicated (antihistamine, acetaminophen)
- No concomitant medications
- Post-Treatment (after last infusion) Evaluations 24 h, 4 wks, 12 wks, 6-Month Follow-Up

Study of Humanized LL2 (Epratuzumab) in pSS

Patient Population

- Males or Females > 18-years-old
- Meet American European Consensus Group Revised Criteria for primary Sjögren's Syndrome (pSS)
- On Symptomatic Treatment > 6 months
- ESR > 25 mm/hr or Hypergammaglobulinemia > 1.4 gm/L
- No High-Dose Steroids/Immunosuppresives within 4 wks
- No Prior Rituximab/Other Anti-B-cell MAb Therapies
- Adequate Laboratories: Hematology (Hgb >10, WBC > 3,000, Plts > 100,000), Renal (Crea < 1.5 ULN), & Liver (Bili < 1.5, ALT,AST, Alk Phos < 2.5 ULN)
- Other Standard Safety Criteria

Study Procedures

- SS Activity: Clinical Signs/Symptoms, Salivary & Lacrimal Function Tests, Autoantibodies, Other Labs
- Toxicities/Adverse Events (NCI CTC v 2.0)
- Vital Signs, Physical Examinations
- Routine Safety Labs (hematology, chemistry, UA)
- Serum Immunoglobulins
- Peripheral blood B and T cells
- hLL2 Levels
- Human Anti-*h*LL2 Antibodies (HAHA)

Study Status

- 10 Pts Enrolled, 10 Completed
  Treatment: 8F / 2M, 38 – 73 years old
- Median Yrs Post Diagnosis: 6 (1-16)
- Median ESR 29 mm/hr
- Median Serum Gammaglobulins 2.3 gm/L
- ANA Positive: 9 pts
- Ro(SS-A) Positive: 8 pts
- La (SS-B) Positive: 7 pts

Study of Humanized LL2 (Epratuzumab) in SLE

Safety Adverse Events

- Infusion Time:
  - Median: 52 minutes (Range: 23 – 86 minutes)
  - No Infusion Reactions
- Adverse Events Reported in 5 Pts
- Dental abscess (resolved, not considered drug related)
- TIA (single episode, not considered drug related)
- Diarrhea/palpitations (grade 1)
- Headache (grade 1)
- Lower limb parasthesia (grade 1)

Study of Humanized LL2 (Epratuzumab) in pSS

Safety

Standard Hematology/Chemistry (N=9)

Parameter	Unchanged from Baseline	CTC Grade 1	CTC Grade 2	CTC Grade 3	CTC Grade 4
		Hematology			
Hemoglobin	9	1	0	0	0
Platelets	9	0	0	0	0
WBC	7	2	0	0	0
		Chemistry			
Creatinine	7	2	0	0	0
T. Bilirubin	9	0	0	0	0
Alk. Phos.	8	1	0	0	0
ALT	9	0	0	0	0
AST	8	1	0	0	0
GGT	9	0	0	0	0

Pharmacokinetics/Immunogenicity

- PK: Serum epratuzumab levels analyzed across infusions (N=4) and after 4th infusion (N=3)
  - Cmax: median 178 µg/mL (range 67 – 272)
  - 7 – 10 day half-life after 4th infusion
  - HAHA: Post-treatment samples analyzed at 24 hours (N=4) and 4 wks (N=2) after 4th infusion
  - No evidence of immunogenicity by ELISA assay sensitive to < 5.0 ng/ml

Study of Humanized LL2 (Epratuzumab) in pSS

B & T CELLS, IMMUNOGLOBULINS

- Consistent Decrease in B Cells After Treatment
- No Consistent Changes in T Cells, IgG, IgA, IgM

	Percent Change from Baseline (Mean +/- SD)	
	24 hours post last infusion	4 weeks
B-cells	-57% +/- 17% (n=5)	-49% +/- 17% (n=3)
T cells	+20% +/- 20% (n=5)	+2% +/- 6% (n=3)
IgG	-7% +/- 10% (n=5)	-11% +/- 12% (n=4)
IgA	0% +/- 11% (n=5)	+5% +/- 8% (n=4)
IgM	-20% +/- 18% (n=5)	-11% +/- 11% (n=4)

Immunomedics, Inc

Study of Humanized LL2 (Epratuzumab) in pSS

Preliminary Efficacy

Component	Abnormal at Baseline	Improved at 24 hours/Evaluated	Improved at 4 wks/Evaluated
Dry/irritated eyes (0-2)	7	4/6	2/4
Dry mouth (0-2)	8	3/7	1/5
Fatigue (0-3)	9	6/8	4/7
Tender joint count (28 joints)	5	4/4	4/4
Tender point count (18 points)	5	3/4	3/3
Schirmer I Test	-	6/8	5/7
Unstimulated salivary flow	-	3/8	3/6

Immunomedics, Inc

Lessons from Clinical Studies in SLE and Sjögren's Disease (Currently 24 patients > 90 infusions)

- Safe and well tolerated in autoimmune disease setting
- Symptomatic improvement in all SLE patients
- Infusion <1 hour without significant infusion reactions (Grade 1 and 2)
- No immunogenicity to date
- Biological efficacy in SLE and Sjögren's diseases in presence of partial B-cell depletion
- Effective without concomitant immunosuppressive medications

Immunomedics, Inc

Pilot Phase II Study of Humanized Anti-CD22 Monoclonal Antibody, hLL2 (Epratuzumab), in Systemic Lupus Erythematosus Therapy

J. Kaufmann[1], W. A. Wegener[2], I.D. Horak[2], J. Kovacs[2], C. Ding[2],

M.U. Qidwai[2], D.M. Goldenberg[2,3], G.R. Burmester[1], T. Dörner[1].

[1]Department of Medicine/Rheumatology and Clinical Immunology, Charite Hospital, Berlin, Germany, [2]Immunomedics, Inc., Morris Plains, NJ, [3]Garden State Cancer Center, Belleville, NJ

→ Rationale / Objectives

- B-cells Play Important Role in Pathogenesis of Autoimmune Disorders
- First Pilot Study of anti-CD22 MAb, hLL2 (*Epratuzumab*, Immunomedics, Inc.), in SLE
- Study Objectives:
  - Confirm Safety,Tolerance and Lack of Immunogenicity in SLE
  - Evaluate Early Evidence of Efficacy in SLE
  - Assess Pharmacokinetics and Pharmacodynamics

→ Study Design

- Open-Label, Non-Randomized Study
- ~15 Pts
- Screening/Baseline Evaluations
- 360 mg/m^2 epratuzumab q 2 wks X 4 Doses; All Pts Premedicated (antihistamine, acetaminophen)
- Post-Treatment (after last infusion) Evaluations 24 h, 4 wks, 12 wks, 6 month Follow-Up

→ Efficacy BILAG

8 Organ-based Systems:

- General (fatigue, fever, anorexia, wt loss, etc.)
- Mucocutaneous (rash, alopecia, mucosal ulcers, etc.)
- Neurologic (headache, seizure, delirium, etc.)
- Musculoskeletal (arthritis, myalgia, etc.)
- Cardiovascular/Respiratory (rub, dyspnea, effusion, etc.)
- Vasculitis (Raynauds, thromboembolism)
- Renal (proteinurea, renal insufficiency, etc.)
- Hematologic (cytopenias, coagulopathy, etc.)

Each Individually Assessed for Activity: 0 – 9 Scale

Global Activity Scale Summed Scores (0 - 72)

→ Patient Population

- Males or Females ≥ 18-years-old
- SLE by ACR Revised Criteria (≥ 4/11 criteria)
- SLE ≥ 6 months
- Moderately Active Disease (6 –12 on BILAG Index)
- No Prior Rituximab/Other Anti-B-cell MAb Therapies
- Adequate Laboratories: Hematology (Hgb > 8, WBC > 2,000, Plts > 50,000), Renal (Crea < 2.5 mg/dL), and Liver (ALT, AST, Alk Phos < 2 X ULN)
- Other Standard Safety Criteria

→ Study Procedures

- SLE Activity: Clinical Signs, Symptoms, SLE Panel (Autoantibodies, C3, CRP, ESR, Other Labs), VAS (global assessment of disease activity, arthralgia, fatigue)
- Toxicities/Adverse Events (NCI CTC v 2.0)
- Vital Signs, Physical Examinations
- Routine Safety Labs (hematology, chemistry, UA)
- Serum Immunoglobulins
- Peripheral Blood B and T cells
- hLL2 Levels
- Human Anti-hLL2 Antibodies (HAHA)

→ Study Population

- 14 Pts Enrolled and Treated
- 13F / 1M, 22 – 52 years old
- Median Yrs Post Diagnosis: 10.1 (1.07-18.6)
- 11 Pts Received 0- 4 Prior Therapies
- Most Frequent Presenting Criteria:
  - 14/14: Antinuclear antibody, Photosensitivity
  - 11/14: Immunologic disorder
  - 10/14: Malar rash
  - 8/14: Hematologic disorder

→ Study Population (con't)

- Disease Activity Levels at Entry
  - BILAG Median Global Scores: 9 (range, 6 - 12)
  - No pts had A-level activity in any system
  - 13/14 pts had B-level activity in ≥ 1 systems:

    typically mucocutaneous, vasculitis, or cardiovascular/respiratory/ no renal or CNS
- Concomitant Medications at Entry
  - Prednisolone, < 10 mg/day (N = 6)
  - Azothioprine, 50-200 mg/day (N = 6)
  - Methotrexate, 15-20 mg/day (N = 3)

Study of Humanized LL2 (Epratuzumab) in SLE

→ Safety

Adverse Events (N=14)

Infusion Time: Median: 31.5 minutes (Range: 23 – 86 minutes)

No Infusion Reactions

Adverse Events Reported

1 Pt: Sleepiness at 1st Infusion. Attributed to IV antihistamine premedication. Pt received 2nd - 4th infusions without event.

1 Pt: Herpes Zoster. Developed after 2nd Infusion and discontinued therapy. Responded to antivirals.

1 Pt: Otitis media. Developed after 4th Infusion. Responded to antibiotics.

Study of Humanized LL2 (Epratuzumab) in SLE

→ Safety

Standard Hematology/Chemistry (N=14)

Parameter	Unchanged from Baseline	CTC Grade 1	CTC Grade 2	CTC Grade 3	CTC Grade 4
Hematology					
Hemoglobin	14	0	0	0	0
Platelets	14	0	0	0	0
WBC	14	0	0	0	0
Chemistry					
Creatinine	11	3	0	0	0
T. Bilirubin	14	0	0	0	0
Alk. Phos.	12	2	0	0	0
ALT	10	1	2 *	1 ‡	0
AST	10	3	1 *	0	0
GGT	12	0	2 *	0	0

* CTC Grade 1 At Baseline ‡ CTC Grade 2 At Baseline

Pharmacokinetics/Immunogenicity

- PK: Measurable serum epratuzumab levels achieved after treatment and 4 weeks later
- HAHA: No evidence of immunogenicity by ELISA assay sensitive to < 25 ng/ml

Time post 4th Infusion	Samples Analyzed	epratuzumab (ug/mL) Mean (range)	HAHA Increase from Baseline
24 hours	12	158 (49-350)	0
4 weeks	7	79 (31-137)	0
12 weeks	6	6.5 (<0.5 – 21)	0

B & T CELLS, IMMUNOGLOBULINS

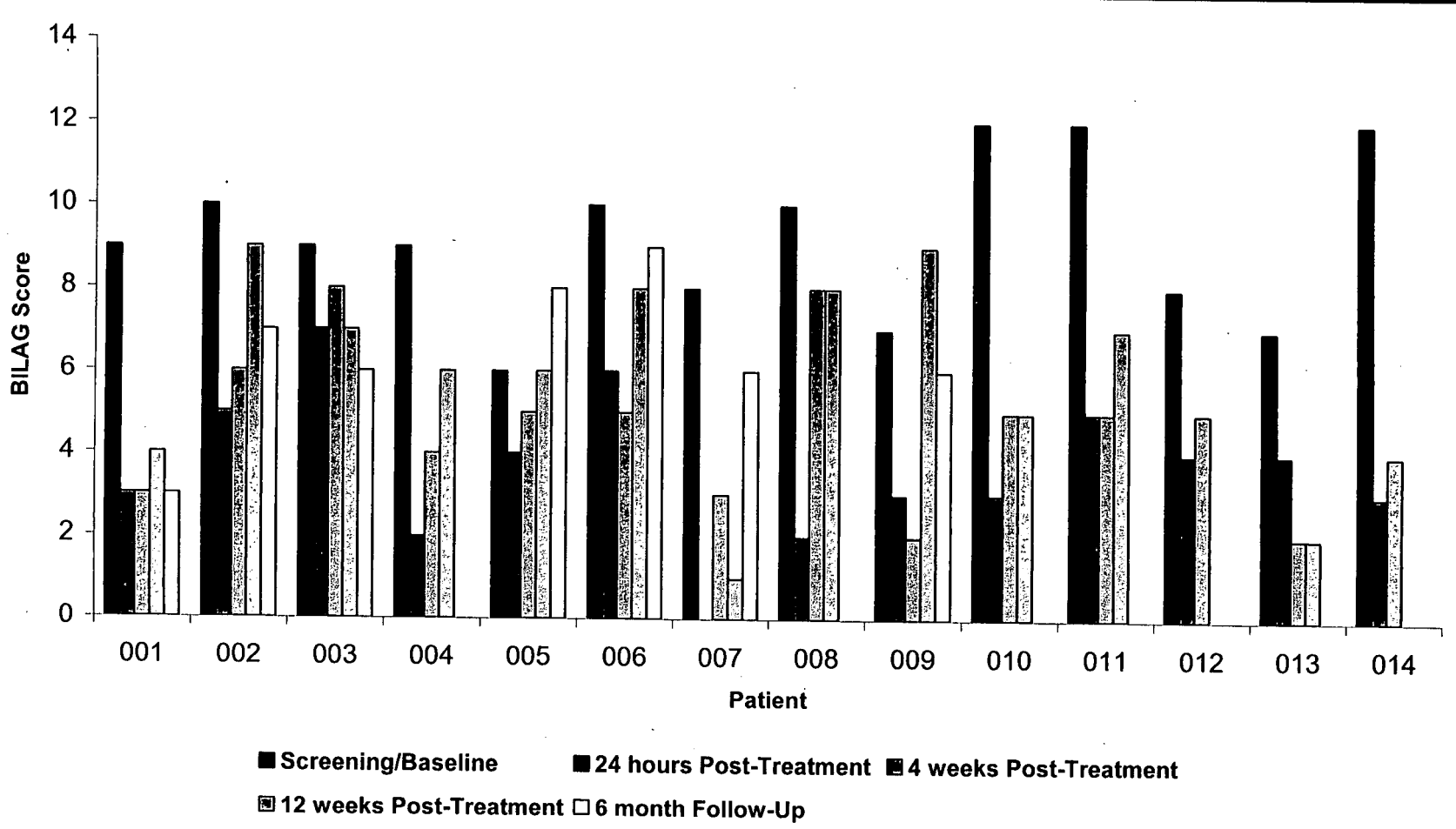
- **Consistent Decrease in B Cells After Treatment**
- **No Consistent Changes in T Cells, IgG, IgA, IgM**

	Percent of Baseline (Mean +/- SD)*			
	24 hours post last infusion	4 weeks	12 weeks	6 months
B-cells	65% +/- 21%	59% +/- 38%	58% +/- 17%	40% +/- 15%
T-cells	116% +/- 73%	128% +/- 73%	97% +/- 45%	76% +/- 28%
IgG	102% +/- 8%	105% +/- 13%	108% +/- 16%	97% +/- 1%
IgA	104% +/- 11%	107% +/- 13%	104% +/- 15%	108% +/- 18%
IgM	86% +/- 16%	96% +/- 21%	88% +/- 13%	87% +/- 8%

*Lymphocytes, 4-8 samples/timepoint; Immunoglobulins, 5-10 samples/timepoint

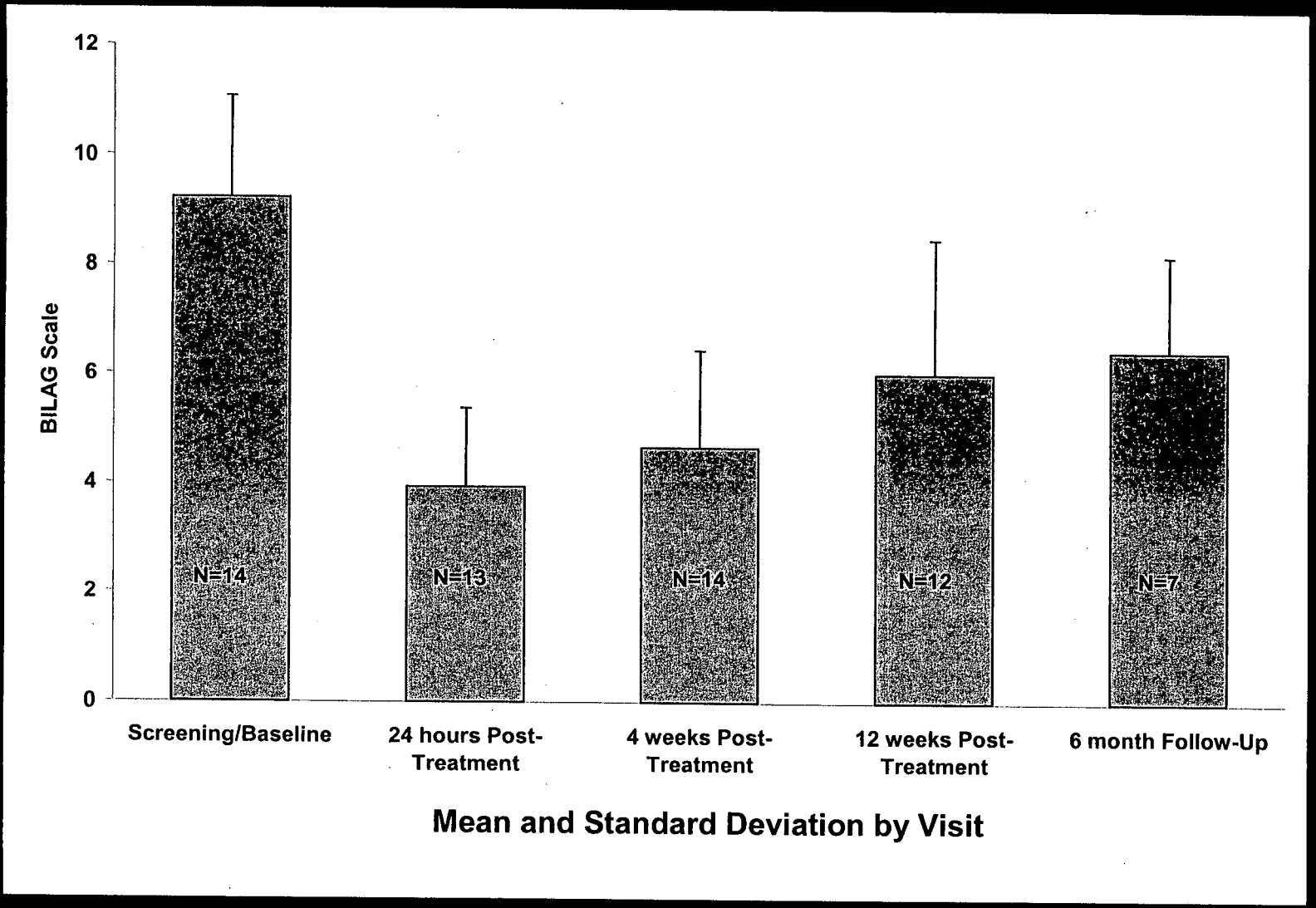
Study of Humanized LL2 (Epratuzumab) in SLE

→ Efficacy Patient Global BILAG Scores



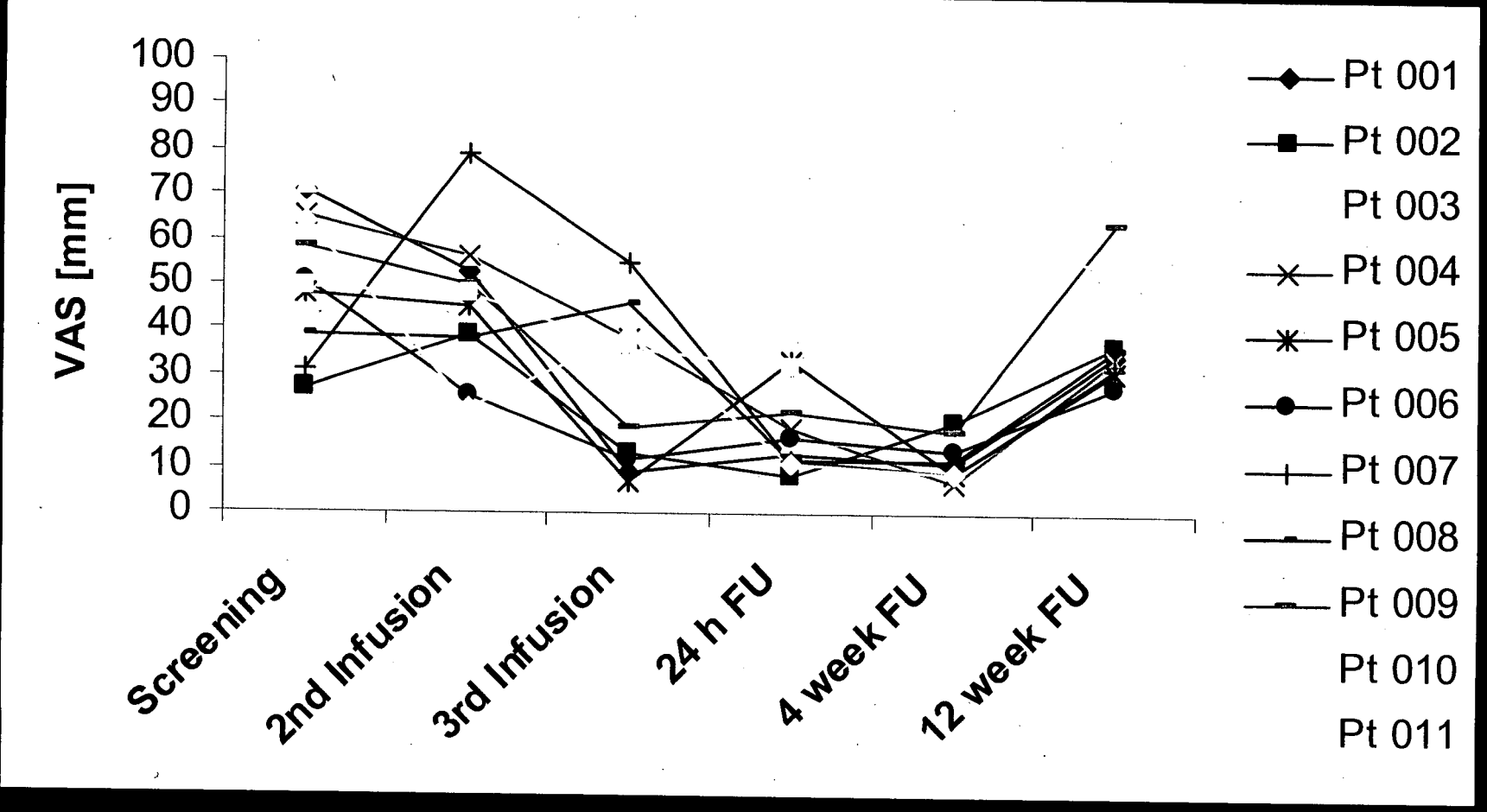
Study of Humanized LL2 (Epratuzumab) in SLE

→ Interim Efficacy Mean BILAG Scores



Study of Humanized LL2 (Epratuzumab) in SLE

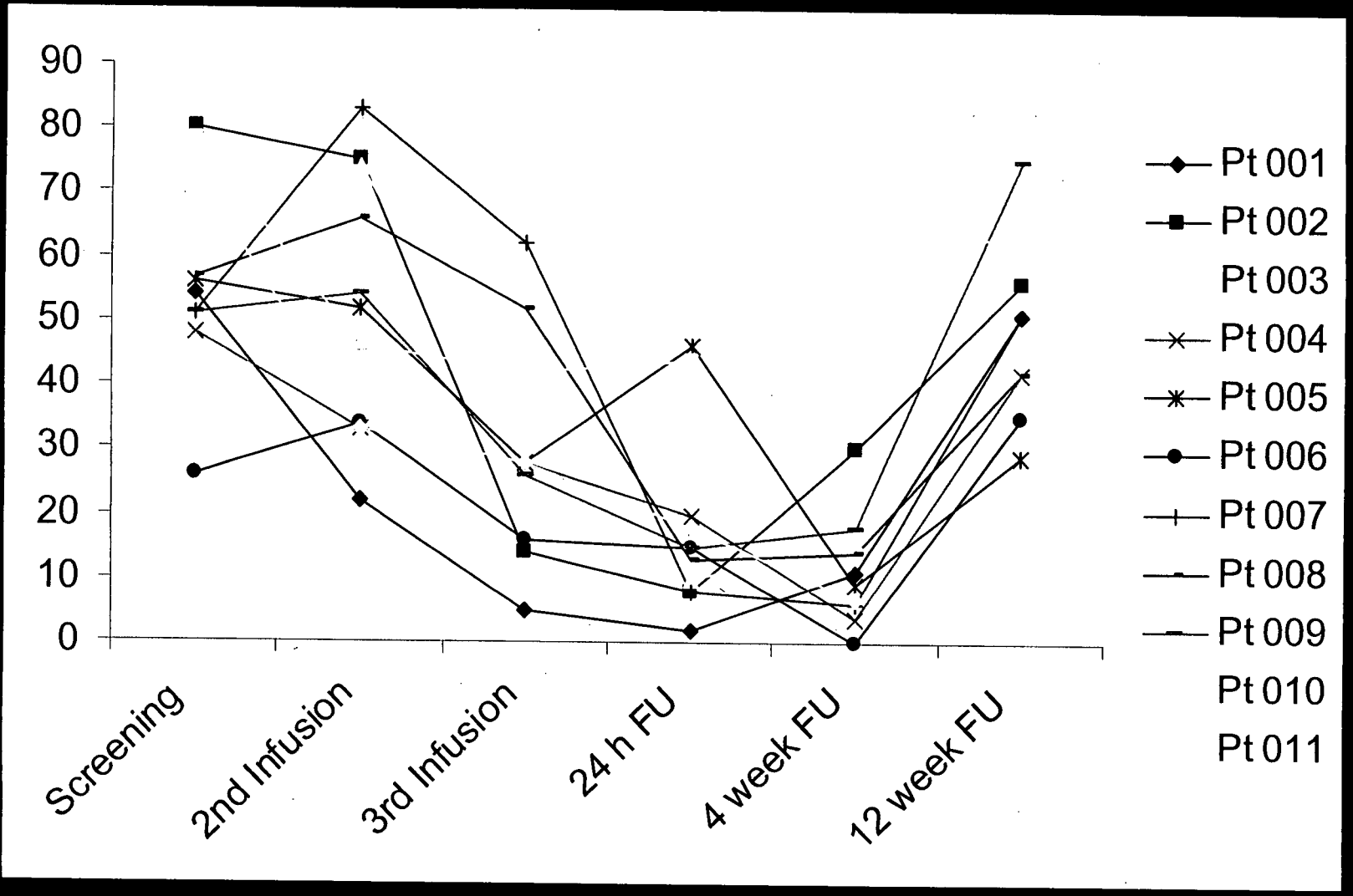
→ Interim Efficacy VAS: Pts. Global Assessement of Disease Activity



Study of Humanized LL2 (Epratuzumab) in SLE

→Interim Efficacy

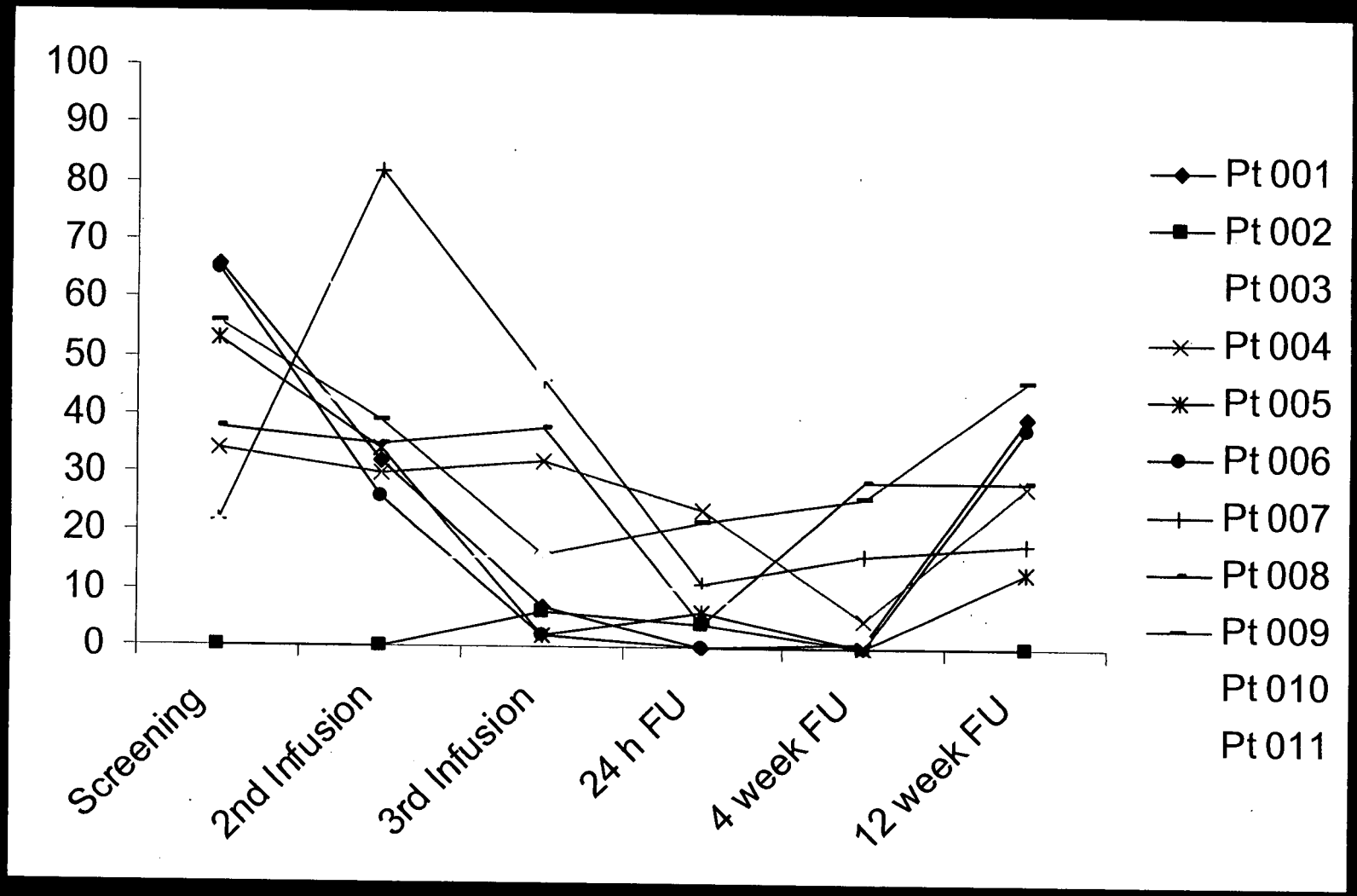
VAS: Fatigue



Study of Humanized LL2 (Epratuzumab) in SLE

→ Interim Efficacy

VAS: Arthralgia



Study of Humanized LL2 (Epratuzumab) in SLE

→ Interim Efficacy

At Screening/Baseline

BILAG Score: 12

After 4th Infusion

BILAG Score: 3

SUMMARY

Epratuzumab (hLL2) Immunotherapy

- Safe and well tolerated
- Symptomatic improvement in all pts
- Administered < 1 hr without significant infusion reactions
- Achieved consistent antibody serum levels, decreased B-cell levels
- No evidence of immunogenicity, T-cell or immunoglobulin alterations

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